RESEARCH ARTICLE

Exploring risk factors for persistent neurocognitive sequelae after hospitalization for COVID-19

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Abstract

Objective: In this study of patients hospitalized during acute SARS-CoV2 infection with 6-months of follow-up data, we identified risk factors associated with the development of neuro-PASC. **Methods**: We conducted an exploratory, observational single-center cohort study of patients hospitalized for COVID-19 from November 2020 to March 2022. Our primary outcome was persistent neurocognitive symptoms, defined as fatigue, headache, loss of taste/smell, brain fog, confusion, concentration/memory/word finding difficulty, and/or change in speech present at 1-month and persisting for 6-months following acute SARS-CoV2 infection. Secondary outcomes included persistent impairment scores on PROMIS cognitive function and abilities scales. Multivariate logistic regression analyses identified potential risk factors for neuro-PASC. **Results**: Of 89 participants, 60% reported persistent neurocognitive symptoms at 6-months; fatigue was the most prevalent, occurring in 53% of participants, followed by brain fog in 34% of participants. Lower self-reported socioeconomic status and increased pre-COVID-19 anxiety scores on the Hospital Anxiety and Depression Scale were associated with increased odds of developing persistent neurocognitive symptoms. Being female and of Hispanic descent were associated with increased odds of persistent cognitive function and ability impairment. **Interpretation**: Sociodemographic factors and pre-COVID-19 anxiety symptoms may be important risk factors for neuro-PASC. These findings underscore the need to assess various sociodemographic factors in research on PASC. Our study also highlights premorbid mental health symptoms as a potential predictor of persistent neurocognitive symptoms following hospitalization with SARS-CoV2 infection.

Introduction

Self-described neurocognitive impairment has been reported in some hospitalized COVID-19 patients following the acute phase of the illness.[1–3] At this stage in the COVID-19 pandemic, there is increasing interest in the chronic or persistent symptoms of the disease, which have been broadly termed as "post COVID-19 condition," "post-acute sequelae SARS-CoV-2 infection (PASC)," or more colloquially, "long COVID." The World Health Organization has defined post COVID-19 condition as sequelae developing in "individuals with a history of probable or confirmed SARS-CoV-2 infection, usually within 3-months from infection onset, with symptoms that last for at least 2-months and that cannot be explained by an alternative diagnosis."[4] Many cohort studies have reported data on the persistence of neurocognitive symptoms for several months after the acute phase of COVID-19.[5–10] However, the criteria used in prior studies to define neurocognitive-PASC (neuro-PASC) are often not based upon these WHO timelines and vary significantly between studies.[10,11] The primary goal of the present study was to identify potential risk factors associated with the development of neuro-PASC

using rigorous criteria based upon the WHO definition for PASC, among survivors of hospitalization for COVID-19. A secondary goal was to identify risk factors for persistent self-reported neurocognitive disturbance, measured by the Patient-Reported Outcome Measurement Information System (PROMIS), including cognitive functioning and abilities in our cohort.[12]

Patients and Methods

Study design and participants

We conducted an observational, exploratory single-center longitudinal cohort study of patients hospitalized for COVID-19 in the University of Washington (UW) hospital system from November 2020 through March 2022. Patients admitted for COVID-19 were identified by screening of inpatient electronic medical records. Inclusion criteria were hospitalization for COVID-19 [verified by a positive real-time polymerase chain reaction (RT-PCR) COVID-19 test result collected via nasopharyngeal swab], age ≥18 years, English proficiency, and survival at 1-month post-hospitalization discharge. Individuals who incidentally tested positive for COVID-19 on routine screening, but in whom COVID-19 was not the primary reason for hospitalization were excluded. Additional exclusion criteria included inability to provide informed consent and history of severe dementia or cognitive impairment limiting independent performance of basic activities of daily living.

Participants who met the above criteria were enrolled via telephone at 1-month after discharge from hospitalization with SARS-CoV2 infection. Participant demographics (age, gender, race, ethnicity, body mass index (BMI), and socioeconomic status, self-reported as either "comfortable," "adequate," or "not enough"), hospitalization course characteristics (number of COVID-19 symptoms out of 26 possible during acute infection, length of stay, whether the patient was vaccinated for COVID-19 prior to their hospitalization, the predominant variant during the hospitalization (defined as alpha for patients hospitalized from March 2020–April 2021; delta for patients hospitalized from May 2021 through November 2021; and omicron for patients hospitalized from December 2021 through March 2022 (the end of recruitment for these analyses)), vaccination status, incidence of delirium while hospitalized, intensive care unit (ICU) admission, need for mechanical ventilation, need for vasopressors, need for extra-corporeal membrane oxygenation (ECMO), treatment with remdesivir, convalescent plasma, therapeutic anti-coagulation, dexamethasone, monoclonal antibodies, ivermectin, tocilizumab, or other medications), and medical history prior to COVID-19 hospitalization

(falls, non-skin cancer, congestive heart failure, coronary artery disease, stroke, rheumatoid arthritis, depression, diabetes, hypertension, asthma/COPD, kidney disease, dialysis, and smoking status) were collected through a combination of self-report and review of the electronic health record.

We also utilized the PROMIS metrics to assess self-reported cognitive function. PROMIS is a collection of person-centered, validated measures developed in partnership with the National Institutes of Health (NIH) to assess patient-reported outcomes with a broad variety of health conditions.[13] Each PROMIS instrument has a calculated T-score that can be compared to a reference population, which is the United States general population for most instruments; a T-score of 50 is indicative of the mean for that measure. For each instrument, PROMIS has defined score ranges that designate mild, moderate, and severe impairment. We analyzed responses to PROMIS Cognitive Function Short Form 4a v2.0 and Cognitive Function Abilities Short Form 4a v2.0 in this study (see Appendix).

Pre-COVID-19 baseline neurocognitive function was assessed retrospectively at the time of the 1-month post-discharge interview. Neurocognitive function was assessed using PROMIS metrics along with symptom-based questionnaires. Surveys assessing persistent symptoms and neurocognitive function were then collected via telephone at 1- and 6-months post-discharge.

Primary outcome

Our primary outcome was the presence of persistent, patient-reported neurocognitive symptoms at 1- and 6-months after COVID-19 hospitalization discharge. By defining neuro-PASC as the development of new neurocognitive symptoms at 1-month that persist at 6-months, the current study reflects the PASC definition put forth by the WHO. The following specific neurocognitive symptoms were assessed. Patients reporting the following symptoms at 1-month *and the same symptom* again at 6-months were considered to have neuro-PASC: (1) fatigue, (2) headache, or (3) loss of taste or smell. Patients were also classified as having neuro-PASC if they reported having *any* (not necessarily the same) of the following residual symptoms at 1-month and at 6-months: (1) brain fog; (2) confusion; (3) difficulty concentrating; (4) memory difficulty; or (5) difficulty with word finding/ changes in speech. These five symptoms were grouped together given their similarity and the potential difference in patient interpretation at different time points.[14–16] Similarly, if patients reported having *either* dizziness or feeling off balance at both 1- and 6-months, they were also classified as having neuro-PASC.[17]

Secondary outcomes

Our secondary outcomes were persistent difficulty with cognitive function and cognitive abilities as assessed by the PROMIS metrics.[12] Patients who had mild (T-score of 40 to 44), moderate (30 to 39), or severe (<30) deficiencies in these scores at 1-month and also at 6-months were considered to have had persistent difficulties.

Standard protocol approvals, registrations, and patient consents

This study was approved by the University of Washington institutional review board. All participants provided informed consent for participation in this study.

Statistical analysis

We used descriptive statistics to compare demographic and clinical variables stratified by our primary outcome of persistent neurocognitive symptoms. We tested differences between categorical variables using chi-square tests where cells were ≥5 participants and Fisher's exact tests where cells were <5. For continuous variables, we tested differences using z-tests. Results were not adjusted for multiple comparisons due to the exploratory nature of the study. We also evaluated the number and proportion of patients who had fatigue, headache, or loss of taste or smell at 1- *and* 6-months, and the number and proportion of patients who had brain fog, confusion, difficulty concentrating, memory difficulty, word finding difficulty/change in speech at 1-month *and* any at 6-months. Lastly, we evaluated how many patients reported having dizziness or loss of balance at both 1-month *and* 6-months.

Next, a univariate logistic regression approach modeled the separate relationships of each clinical and acute illness risk factor with the presence of persistent neurocognitive symptoms at 6-months follow-up. Multivariate logistic regression then modeled the associations of significant ($p \leq 0.1$) risk factors in univariate models with each neurocognitive outcome at 6-months.[18] Statistical significance in multivariate models was defined as $p < 0.05$.

Results

Patient baseline and hospitalization characteristics

Out of 255 total eligible participants, 95 could not be contacted, 71 declined to participate, and 89 were enrolled in this study. 54 (61%) were male, 35 (39%) were female (Table 1). The mean age was 53.9 ± 15.5 years, with 21 (24%) being 65 years or older.

Twenty (22%) participants were non-White. The mean body mass index (BMI) was 34.0 ± 9.9 kg/m. Twelve participants (13%) reported an "inadequate" socioeconomic status.

Of the 89 participants, 53 (60%) reported persistent neurocognitive symptoms at 6-months follow-up (Table 1). We found "fatigue" to be both the most reported symptom initially [$n = 51$ (57%)] and at the 6-month follow-up time point [$n = 47$ (53%)] (Table 2). Forty (45%) participants reported fatigue at both 1-month and 6-months post-discharge. We also found certain symptoms were present in participants at 6-months but not at 1-month; for example, "confusion" was observed in 22% ($n = 20$) of patients at 6-months but none at 1-month.

Clinical variables, stratified by whether the patients had persistent neurological symptoms, are presented in Table S1. The number of initial symptoms were not significantly different between those with and without persistent neurocognitive symptoms (5.6 ± 2.3 vs. 5.1 ± 2.4, $p = 0.29$). A longer hospital stay ($p = 0.047$), a need for intubation ($p = 0.004$) and experiencing delirium during the index hospitalization ($p = 0.01$) were more common among those with than without persistent neurocognitive symptoms. Vaccination for COVID-19 at the time of hospital admission and percentage of participants needing ICU admission were similar between the groups. We did not observe significant differences in the proportions of patients with comorbidities between the groups. Similarly, no therapies used to treat COVID-19 (remdesivir, convalescent plasma, therapeutic anti-coagulation, dexamethasone, monoclonal antibodies, ivermectin, tocilizumab, other) during hospitalization were associated with neuro-PASC.

PROMIS cognitive function and cognitive function abilities scale scores were significantly worse among patients with persistent neurological symptoms at 1-month [52.0 ± 8.9, 43.6 ± 10.4, $p = 0.0002$), (52.7 ± 8.5, 45.0 ± 7.9, $p < 0.0001$)] and 6-months [(53.4 ± 7.8, 45.4 ± 8.0, $p < 0.0001$), (54.3 ± 7.5, 48.8 ± 8.3, $p = 0.002$)] compared to patients who did not have persistent neurological symptoms (Table S1).

We did not observe statistically significant differences between the groups on PROMIS fatigue scores, Hospital Anxiety and Depression Scale – Anxiety Subscale, or Hospital Anxiety and Depression Scale – Depression Subscale baseline patient reported outcome measures.

Regression analyses of potential risk factors for persistent neurocognitive symptoms post-COVID-19 hospitalization discharge

In univariate analyses, intubation [5.42 (1.66, 17.67)] and delirium during index hospitalization [5.78 (1.21,

Table 1. Participant demographics stratified on presence of persistent neurocognitive symptoms[1] at 6-months.

N (%) or mean ± standard deviation (SD)	No persistent neuro symptoms n = 36	Persistent neuro symptoms n = 53	Total n = 89	p-value
Age in years, mean ± SD	57.4 ± 15.9	51.5 ± 14.9	53.9 ± 15.5	0.04
Age ≥65 years	12 (33)	9 (17)	21 (24)	0.07
Sex				
Female	11 (31)	24 (45)	35 (39)	0.16
Male	25 (69)	29 (55)	54 (61)	
Race				
Black or African American	3 (8)	2 (4)	5 (6)	
American Indian or Alaska Native	0	2 (4)	2 (2)	
Asian	4 (11)	2 (4)	6 (7)	
Native Hawaiian or Other Pacific Islander	3 (8)	2 (4)	5 (6)	0.37
White	25 (69)	44 (83)	69 (78)	
Other/not reported	1 (2)	1 (2)	2 (2)	
All non-white	11 (31)	9 (17)	20 (22)	0.13
Ethnicity				
Hispanic or Latino	1 (3)	6 (11)	7 (8)	0.23
Body mass index (BMI)[2]	32.6 ± 8.1 (n = 34)	35.0 ± 10.9 (n = 50)	34.0 ± 9.9 (n = 84)	0.43
<24.9 (ideal/underweight BMI)	7 (21)	8 (16)	15 (18)	
25.0–<30 (overweight)	10 (29)	9 (18)	19 (23)	
30–39.9 (obese)	9 (26)	23 (46)	32 (38)	0.31
>40 (morbidly obese)	8 (24)	10 (20)	18 (21)	
BMI ≥ 30	18 (51)	33 (66)	51 (60)	0.18
Socio-economic status				
Comfortable	23 (64)	25 (47)	48 (54)	
Adequate	12 (33)	17 (32)	29 (33)	**0.03**
Not enough	1 (3)	11 (21)	12 (13)	

Bolded values were only to emphasize statistically significant p-value.

[1]In order to be classified as having persistent neurological symptoms, patients had to have had reported *any of the following*: (1) fatigue at 1 *month* and at 6 months; (2) headaches at 1 month *and* at 6 months; (3) loss of taste or smell at 1 month *and* at 6 months; (4) *any* of brain fog, confusion, difficulty concentrating, memory difficulty, or word finding difficulty/change in speech at 1 month *and* at 6 months; or (5) *either* feeling off balance or dizziness 1 month *and* at 6 months.

[2]BMI missing for five participants.

*p < 0.05

27.58)] were associated with persistent neurocognitive symptoms. Being female [7.11 (2.53, 20)] and having an increased baseline Hospital Anxiety and Depression Scale – Anxiety subscale score [1.31 (1.05, 1.63)] were associated with persistent cognitive function disturbance.

Every increased year of age was associated with a 3% decrease (95% CI: 0%–5% decrease) in the odds of having persistent neurocognitive symptoms at 6 months, a 3% decrease (95% CI: 0%–6% decrease) in the odds of having persistent cognitive function disturbance at 6 months, and a 5% decrease (95% CI: 1%–8% decrease) in the odds of having persistent cognitive ability disturbance at 6 months (Table S2). Being female [5 (1.43, 17.54)], Hispanic [9.6 (1.87, 49.32)], and having an increased baseline Hospital Anxiety and Depression Scale – Depression Subscale score [1.36 (1.02, 1.80)]

were also associated with persistent cognitive abilities disturbance.

In multivariate analyses (Table 3), "not enough" [OR: 46.4; 95% CI: (3.4, 627.1)] perceived socioeconomic status was associated with persistent neurocognitive symptoms. Having renal disease was also associated with a decreased risk of persistent neurocognitive symptoms [OR: 0.08; 95% CI: (0.01, 0.72)]. Increased baseline Hospital Anxiety and Depression Scale – anxiety subscale score was predictive of persistent neurocognitive symptoms [OR: 1.5; 95% CI: (1.1, 2.1)].

For PROMIS cognitive function outcomes, female sex was significantly associated with persistent cognitive function disturbance [OR: 5.4; 95% CI: (1.5, 20.2)]; Hispanic ethnicity [OR: 11.4; 95% CI: (1.7, 77.4)] was significantly associated with persistent cognitive ability disturbance (Table 3).

Table 2. Number and percentages of patients with each neurocognitive symptom initially, at 1-month, 6-months, and at 1- and 6-months.

Symptom, n (%)	Initially	1-month	6-months	1- and 6-months[1]
Fatigue	51 (57)	64 (72)	47 (53)	40 (45)
Headaches	21 (24)	25 (28)	17 (19)	11 (12)
Loss of taste or smell	15 (16)	16 (18)	11 (12)	10 (11)
Brain fog	6 (7)	26 (29)	30 (34)	10 (11)
Confusion	7 (8)	0	20 (22)	0
Difficulty concentrating[2]	–	18 (20)	25 (28)	8 (9)
Memory difficulty[2]	–	19 (21)	29 (33)	11 (12)
Word finding difficulty, change in speech[2]	–	14 (16)	29 (33)	10 (11)
Any brain fog, confusion difficulty concentrating, memory difficulty, word finding difficulty/change in speech	–	40 (45)	47 (53)	29 (33)
Feeling off balance[2]	–	17 (19)	24 (27)	10 (11)
Dizziness	13 (15)	23 (26)	21 (24)	9 (10)
Any dizziness/feeling off balance		32 (36)	31 (35)	18 (20)

[1]In order to be classified as having persistent neurological symptoms, patients had to have had reported *any of the following*: (1) fatigue at 1 *month* and at 6 months; (2) headaches at 1 month *and* at 6 months; (3) loss of taste or smell at 1 month *and* at 6 months; (4) *any* of brain fog, confusion, difficulty concentrating, memory difficulty, or word finding difficulty/change in speech at 1 month *and* at 6 months; or (5) *either* feeling off balance or dizziness 1 month *and* at 6 months.

[2]Difficulty concentrating, memory difficulty, word finding difficulty/change in speech, and feeling off balance not queried among initial symptoms.

Table 3. Odds ratios (ORs), 95% confidence intervals (95% CIs), and p-values from multivariate analyses using variables where $p \leq 0.10$ in univariate analyses in Table S2.

	Persistent neurocognitive symptoms (neuro-PASC) OR (95% CI)	*p*-value	Persistent cognitive function disturbance OR (95% CI)	*p*-value	Persistent cognitive ability disturbance OR (95% CI)	*p*-value
Age (continuous)	1.04 (0.99, 1.09)	0.10	1.00 (0.96, 1.04)	0.91	0.98 (0.93, 1.04)	0.53
Female sex	–	–	5.4 (1.5, 20.2)	**0.01**	4.4 (0.8, 24.7)	0.09
Hispanic vs non-Hispanic ethnicity	–	–	3.9 (0.6, 26.7)	0.17	11.4 (1.7, 77.4)	**0.01**
Socioeconomic status						
Comfortable	Referent					
Adequate	2.2 (0.6, 8.2)	**0.01**	–	–	–	–
Not enough	46.4 (3.4, 627.1)		–	–	–	–
Initial symptom: fatigue vs no fatigue	2.0 (0.6, 6.5)	0.24				
Length of stay in hospital (days)	1.01 (0.97, 1.06)	0.63	–	–	–	–
Intubation	7.2 (0.9, 60.5)	0.07	–	–	–	–
Days in ICU	–	–	–	–	1.03 (0.97, 1.08)	0.37
Delirium during index hospitalization	1.6 (0.2, 12.4)	0.68	–	–	–	–
Depression	4.9 (0.7, 36.0)	0.11	2.9 (0.6, 12.9)	0.17	–	–
Renal disease	0.08 (0.01, 0.72)	**0.02**	–	–	–	–
Baseline Hospital Anxiety and Depression Scale – Anxiety Subscale	1.5 (1.1, 2.1)	**0.01**	1.1 (0.8, 1.4)	0.54	–	–
Baseline Hospital Anxiety and Depression Scale – Depression Subscale	–	–	1.1 (0.8, 1.5)	0.46	1.2 (0.8, 1.7)	0.34

Bolded values were only to emphasize statistically significant *p*-value.

Discussion

In this single-center observational cohort study, we assessed potential risk factors for developing neuro-PASC, determined using well-defined clinical criteria. We also evaluated risk factors for decreased patient-reported cognitive function using the validated PROMIS measures.

Ultimately, we identified several potential risk factors, most of which are sociodemographic factors.[19,20] Notably, we identified female sex, Hispanic ethnicity, and lower self-reported socioeconomic status as factors associated with increased risk of developing neuro-PASC in our cohort. These findings identify populations that may be at increased risk for developing cognitive sequalae

following hospitalization with SARS-CoV2 infection and emphasize the importance of including diverse sociodemographic participants in future PASC research.

We found that at 6-months, 53 out of 89 (60%) of our participants reported experiencing persistent neurocognitive symptoms following hospitalization for COVID-19. This finding corroborates those in other studies of persistent neurocognitive symptoms in hospitalized COVID-19 cohorts.[8,9,21] While PASC has been broadly defined, the specific qualifiers for neurocognitive symptoms associated with PASC (neuro-PASC) vary across the literature.[5,22,23] Thus, we defined neuro-PASC using recent WHO guidelines. Use of a rigorous definition of neuro-PASC as well as inclusion of patient-reported assessments of persistent cognitive dysfunction, from a diverse group of hospitalized patients enhances the reproducibility and generalizability of our findings.

We observed a longer length of hospitalization among those with [18 (7, 29.5) days] compared to those without [7 (5,19) days] persistent neurocognitive symptoms. Hospital stay length has been identified in other studies as a risk factor for PASC.[7,24,25] Similarly, the need for intubation and history of in-hospital delirium were more commonly observed in those that developed neuro-PASC and each was separately associated with over five times increased odds of neuro-PASC in our univariate models. In agreement with our findings, intubation and in-hospital delirium has also been previously reported as risk factors for developing neuro-PASC.[8,9] Our findings suggest that these three hospitalization factors may be useful in identifying patients hospitalized with SARS-CoV2 infection at risk for neuro-PASC. Of note, these factors did not remain significant in our multivariate analyses.

When considered in the context of our cohort with more severe disease presentation and hospitalization with SARS-CoV2 infection, our findings may reflect another known entity, post-intensive care syndrome (PICS).[26] In particular, our finding that in-hospitalization delirium is a risk factor for persistent neurocognitive dysfunction supports this hypothesis and suggests that the cause of neurocognitive dysfunction may originate during the acute phase of severe COVID-19 infection. These data corroborate published meta-analyses which demonstrate that delirium is the most consistent clinical risk factor for cognitive impairment following ICU admission for any cause.[27,28]

A higher Hospital Anxiety and Depression Scale anxiety (HADS-A) score at baseline was associated with persistent neurocognitive symptoms in our cohort, suggesting a possible association between premorbid anxiety symptom severity and risk of neuro-PASC. However, we note that the scoring of HADS-A is out of 21 points, in which a range from 0–7 indicates normal/no anxiety and our

cohort scores ranged from 1.1 to 2.1 (Table 3).[29] While this association is statistically significant, it may not be clinically meaningful given the small magnitude of the effect. Larger studies focused on depression and anxiety as potential risk factors for developing neuro-PASC have been done and have found that psychological distress prior to being infected may be associated with post-COVID-19 conditions.[30]

We also found that female sex was associated with greater than five times increased odds of persistent cognitive ability disturbance and greater than seven times increased odds of persistent cognitive function disturbance. Other studies have also found females to be significantly more likely to report persistent neurocognitive symptoms following SARS-CoV2 infection.[21,31–35] One study suggests that discrepancies in sex hormones related to inflammatory processes may also contribute to this difference we see in COVID-19 response.[36] The expression of angiotensin-converting enzyme-2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) receptors, both of which are likely involved in COVID-19 pathogenesis, has also been suggested to differ between the sexes and may play a role in the long-term effects of COVID-19.[37] However, the biological differences between females and males and their role in developing neuro-PASC have yet to be fully elucidated. Furthermore, non-biological factors may also be associated with female sex and may contribute to the observed associations. Further subgroup analyses did not demonstrate significant differences in demographic or clinical factors between sexes (data not shown).

We observed a statistically significant association between the history of renal disease and decreased odds of neuro-PASC. This finding was unexpected given the observations of an association between renal disease and increased risk of adverse COVID-19 outcomes.[36,38–41] Thus, this association should be interpreted cautiously given multiple comparisons in our exploratory analyses and requires further study.[36,38–41]

We also found that self-reported socioeconomic status (SES) is associated with risk of neuro-PASC ($p = 0.03$). Participants that reported a status of "not enough" socioeconomic resources had 46 times increased risk of developing neuro-PASC compared to those who reported "comfortable" SES. Notably, these categories were defined by each participant's subjective perspective of their socioeconomic resources, rather than an objective measure such as area deprivation index or income brackets. This suggests that subjective experience may be an important element to consider in the clinic setting and in future patient-reported outcomes research. This finding corroborates other reports in the literature that socioeconomic status plays an important role in developing more severe and long-lasting COVID-19 outcomes.[36,42,43]

Hispanic ethnicity was associated with greater than 11 times increased risk of persistent cognitive ability disturbance as defined by the PROMIS measure ($p = 0.01$). Hispanic individuals have been disproportionately adversely affected by the COVID-19 pandemic.[44] This is a historically vulnerable group that has high rates of comorbidities, decreased access to healthcare, language barriers, food insecurity, higher rates of essential workers status, and numerous other factors that ultimately have led to worse outcomes, including higher infection rates, hospitalizations, and mortality, with COVID-19.[45] An increased risk of adverse COVID-19 outcomes has also been noted among Black populations.[46] Our data add to these findings and demonstrate that Hispanic participants may face an increased risk for developing neuro-PASC. We argue that this population may warrant closer follow-up after hospitalization with COVID-19. In contrast, others have found that White populations were more likely to develop prolonged COVID-19 symptoms; further studies with diverse cohorts are needed to clarify the association between social determinants of health among different racial groups and post-COVID-19 outcomes.[34]

It is important to note that, while the potential risk factors identified in our study were primarily psychosocial factors, there are likely other components such as the presence of persistent viral antigen or inflammation that may also contribute to neuro-PASC risk and were not assessed in the present study.[47] Future studies focused on biomarkers for neuro-PASC will build upon the current findings and improve our understanding of the pathogenesis of neuro-PASC.[47]

There are limitations to this current study. First, this is an exploratory, hypothesis-generating analysis and our findings need to be confirmed in future studies designed to test these specific hypotheses. This analysis is not intended to examine causality. Rather than implying that the potential risk factors are causing the outcome (i.e., neuro-PASC), we aimed to determine whether these risk factors may be associated with the outcome. The available sample size of 89 participants does not permit larger multivariate regression models including all potential factors of interest. Thus, we instead performed pre-screening analyses with univariate regression models using a liberal p-value cut-off of $p < 0.1$. Second, the relatively small sample size may limit power in the analyses conducted. Third, this is a single-center study based at an academic medical center in Seattle, Washington. Thus, whether the findings may be generalized to other populations is not known. Fourth, we do not have information on the eligible individuals that declined to enroll in the study; therefore, we are unable to generalize the observed trends from our cohort to broader populations of individuals

hospitalized for COVID-19. Fifth, the pre-COVID-19 baseline patient reported outcomes were collected 1-month post-hospitalization discharge, thus these data are subject to recall bias. Sixth, the lack of a control group of individuals hospitalized for a non-COVID condition prevents us from comparing differences to a benchmark population. Seventh, objective measures of cognitive performance or reported persistent neurologic symptoms were not included in this study, most factors were patient-reported. Further studies with a larger sample size, multiple centers, control groups, and objective measures are needed to understand the full extent of risk factors associated with the development of neuro-PASC. Eighth, results were not adjusted for multiple comparisons because of the exploratory nature of the study.

Strengths of our study include the use of a rigorous symptom-based definition of neuro-PASC as well as validated patient-reported measures of cognitive dysfunction (PROMIS), inclusion of a relatively racially and ethnically diverse population, incorporation of detailed clinical risk factors drawn from the electronic health record, and longer follow-up than reported in many prior similar studies.

Ultimately, our study suggests that sociodemographic factors may be important risk factors for developing neurocognitive PASC. Female sex, Hispanic ethnicity, and lower perceived socioeconomic status were each associated with increased risk of neuro-PASC in a diverse cohort of adult survivors of hospitalization for COVID-19. We argue that these findings underscore the need to include sociodemographic factors, including measures of social determinants of health, in future studies of neuro-PASC and that these factors may help identify patient populations at particular risk of neuro-PASC who may benefit from increased clinical attention.

Author Contributions

All authors provided essential contributions to this manuscript in its present form. Peter Y. Ch'en wrote the initial draft of the manuscript and led the team in its revisions. Laura S. Gold provided statistical analysis for the manuscript. Qiongshi Lu and Ting Ye provided additional statistical expertise to ensure robust methodology. James Andrews and Payal Patel provided mentorship and expertise in the formation and revisions of this manuscript and study.

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Conflict of Interest

No conflicts of interest to disclose.

Data Availability Statement

Anonymized data not published within this article will be made available upon reasonable request.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1.
Appendix S1.